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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,849	03/30/2004	Todd Zankel	30610/40037	3684
4743 7590 08/14/2008 MARSHALL, GERSTEIN & BORUN LLP 233 S. WACKER DRIVE, SUITE 6300 SEARS TOWER CHICAGO, IL 60606			EXAMINER KOLKER, DANIEL E	
			ART UNIT 1649	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/812,849

Applicant(s)

ZANKEL ET AL.

Examiner

DANIEL KOLKER

Art Unit

1649

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-19, 21, 22 and 58-62 is/are pending in the application.
- 4a) Of the above claim(s) 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-19, 21, 58-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S5108)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The remarks and amendments filed 21 April 2008 have been entered. Claims 17 – 19, 21 – 22, and 58 – 62 are pending.

Election/Restrictions

2. Claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 21 June 2006.
3. Claims 17 – 19, 21, and 58 – 62 are under examination.

Withdrawn Rejections and Objections

4. The following rejections and objections set forth in the previous office action are withdrawn:
 - A. The objection to claim 17 for recitation of "RAP" without first defining the abbreviation is withdrawn in light of the amendment.

New Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 – 18 and 58 – 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A similar rejection was made in the office action mailed 31 August 2006 (see paragraph number 7 on p. 4), and was withdrawn in the office action mailed 9 July 2007 (see paragraph 5B on p. 2). Upon further consideration and careful review of the newly-disseminated written description training materials, available on the USPTO's website at <http://www.uspto.gov/web/menu/written.pdf>, this rejection is reinstated.

Independent claims 17 – 18 are drawn to administration of a fusion protein comprising a RAP fragment. In both of these claims, the fragment can vary from residues 221 – 323 of SEQ ID NO:1 by as much as 20% and must also bind to megalin (also known as LRP2, see p. 34 line 21 of the specification). The specification states (p. 39), that LRP binding fragments are preferred, and lists several non-overlapping RAP fragments, including residues 221 – 323.

The specification fails to disclose which regions within residues 221 – 323 of SEQ ID NO:1 are either necessary or sufficient for LRP2 binding to be maintained. The factors to be considered in determining whether a claimed invention meets the written description requirement of 35 USC § 112, first paragraph, include but are not limited to, actual reduction to practice, description of complete or partial structure, formulas or drawings of the invention, and identifying characteristics; see MPEP § 2163(II). In the instant case, the specification fails to show actual reduction to practice of variants at least 80% identical to residues 221 – 323 of SEQ ID NO:1 which retain LRP2 (that is, megalin) binding. There is not actual reduction to practice of the full invention encompassed by the claims (note that while the claims are drawn to methods, discussion here is with respect to the products which are required to be administered in these methods). The specification does not provide description of which regions within residues 221 – 323 are to be varied or are to be deleted such that megalin (LRP2) binding is maintained. That is, the specification fails to describe structures common to all members of the genera claimed. The specification fails to provide description of the megalin binding region.

While a declaration filed under 37 CFR § 1.132 by Dr. Zankel on 5 March 2007 discloses the results of an experiment that measured LRP2 binding, the fragment used there was residues 201 – 319 of SEQ ID NO:1 (declaration, paragraphs 3 and 6). This is not a fragment that is 80% identical to residues 221-323; it is considerably closer in identity than that as it includes all of residues 221 – 323, with the exception of the four C-terminal residues. Additionally, the data presented in the declaration fail to show which 20% of the residues can be deleted or changed, such that LRP2 binding is retained, as encompassed by claims 17 and 18. Because the specification does not show a correlation between the structure (variation from residues 221 - 323 of SEQ ID NO:1) and function (binding to LRP2, also known as megalin) as recited in claims 17 - 18, the written description requirement has not been met.

Applicant is directed to the newly-disseminated written description training materials, available on the USPTO's website at <http://www.uspto.gov/web/menu/written.pdf>, for additional information on the written description requirement. Pages 1 – 2, which provide an overview of

the office's interpretation of this requirement, as well as pages 37 – 39, drawn to variants of nucleic acid and protein expressed in terms of percent identity and function, where neither the art nor the specification discloses a correlation between structure and function, are particularly on point. Amendment of claims 17 – 18 to read "...consisting of the amino acid sequence of residues 221 – 323 of SEQ ID NO:1..." would be sufficient to overcome this rejection.

For the reasons above, claims 17 – 18 are rejected. Claims 58 – 62 depend from these claims in the alternative and therefore are rejected as well. Note claim 19, drawn to administration of a RAP polypeptide consisting of an amino acid sequence at least 80% identical to residues 221 - 323 of SEQ ID NO:1 is not subject to this rejection. Claims to proteins or fragments thereof identified by sequence homology are considered described; see Example 11 of the written description training materials.

Maintained Rejections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 – 19, 21, and 58 – 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardridge (2002. Nature Reviews Drug Discovery 1:131 – 139) in view of Fillebeen (1999. Journal of Biological Chemistry 274:7011 – 7017, cited as reference C12 on the IDS filed 18 June 2004), Neels (1999, Journal of Biological Chemistry 274:31305 – 31311,

cited as reference C85 on the IDS filed 5 March 2007), and Saenko (WO 00/71714, cited in office action mailed 9 July 2007).

The reasons why the specific limitations of claims 17 - 19, 21, and 58 - 62 are met by the cited references have been set out in detail in the previous office action. Briefly, Pardridge teaches chimeric proteins are useful for treatment of many disorders when it is necessary to deliver a therapeutic compound across the blood-brain barrier (BBB), and teaches that use of a vehicle will enhance drug delivery across the BBB. Pardridge explicitly teaches that BDNF, recited in claims 61 - 62, is therapeutic for stroke, suggesting that it should be conjugated to BBB-transport vehicle in order to increase entry into the brain. However Pardridge does not teach conjugates comprising RAP fragments, as recited in independent claims 17 - 19.

Fillebeen teaches experiments in which an *in vitro* model of the BBB (bovine brain capillary endothelial cells, BBCEC) was used to determine whether or not lactoferrin is brought across the BBB and if so what receptor brings it across the BBB. On p. 7016, the reference also teaches that the transcytosis is inhibited by including receptor associated protein (RAP) in the assay, and that RAP binds to and inhibits the actions of low-density lipoprotein receptor (also called LRP). Fillebeen concludes that the experiments indicate that LRP is responsible for the transcytosis of the ligand across the BBB. However while Fillebeen teaches that RAP binds LRP and that LRP mediates transcytosis, the reference does not explicitly teach administration of conjugates comprising RAP for increasing transport across the BBB and does not teach conjugates comprising RAP fragments, as recited in independent claims 17 - 19.

Neels teaches that LRP receptor has four ligand-binding clusters, and that RAP binds to clusters II - IV of LRP (see data summarized in Table 1). Neels also teaches that LRP binds to and internalizes a number of ligands, which are structurally diverse, including apolipoproteins, lipases, proteinases, proteinase-inhibitor complexes, lactoferrin, and an endotoxin, amongst others (see p. 31305, top of second column). Given the diversity of ligands that Neels teaches are both bound *and* internalized by LRP, it is clear that the structures of the ligands what allows them to be both bound and internalized. Those molecules which have structural elements which permit them to bind to LRP will all be expected to be internalized. While all the data from the experiments reported by Neels are on point to binding and do not mention internalization, given that Neels teaches that the receptor was well-known to bind and internalize a very diverse set of ligands, an artisan of ordinary skill would, upon reading the reference, clearly understand that those ligands which bind are internalized. However Neels does not teach administration of

conjugates comprising RAP for increasing transport across the BBB as recited in independent claims 17 – 19.

Saenko teaches RAP fragments which bind to LRP. See for example p. 29 first paragraph. Saenko teaches that residues 203 – 319 of RAP constitute the receptor-binding region of RAP; See p. 30 first complete paragraph. This fragment is more than 80% identical to residues 221 – 323 of SEQ ID NO:1. It is within the scope of fragment recited in independent claims 17 – 19, and is evidenced to bind the LRP receptor. While the reference is silent as to whether this fragment will bind megalin (also known as LRP2), the reference provides motivation to select this particular fragment, as it binds RAP. Absent evidence to the contrary, the fragment is presumed to have the property of binding megalin, as it meets all structural limitations recited in independent claims 17 – 19. However Saenko does not teach administration of conjugates comprising this fragment to subjects as recited in claims 17 – 19.

It would have been obvious to one of ordinary skill in the art to make a fusion protein between a therapeutic agent, such as BDNF as taught by Pardridge, and the RAP fragment consisting of residues 203 – 319 as taught by Saenko, and to administer this compound to patients in order to increase the transport of the agents across the BBB, i.e. for therapy for stroke. This motivation comes directly from the prior art references themselves. Pardridge teaches that this method (conjugating agents to transport vehicles) is useful for increasing transport of the agents across the BBB and also teaches that BDNF should be used to treat stroke in humans; Fillebeen teaches that RAP is a LRP-binding molecule and that transports molecules across the BBB; Neels teaches that those agents (such as RAP) which bind to LRP are expected to be internalized, which of course is a necessary step in the LRP-mediated transcytosis taught by Fillebeen. Finally, Saenko provides guidance for selecting the specific RAP fragment (residues 203 – 319) which is within the scope of the fragments recited in claims 17 – 19, as the LRP-binding region.

On pp. 4 - 10 of the remarks filed 21 April 2008, applicant argues extensively that the examiner has improperly combined the teachings of the cited references to arrive at the conclusion of obviousness, and argues that the LRP2-binding property recited in independent claims 17 – 19 have not been provided and may or may not be present. Specifically, applicant makes the following arguments, each of which will be addressed in turn:

- 1) The examiner is mistaken in assuming that any and all LRP ligands will cross the blood-brain barrier (remarks, p. 5, final paragraph), and that data from other references support

applicant's arguments that RAP does not bind to this receptor in the same manner as other ligands.

2) The examiner is mistaken in assuming that "regions of RAP that bind LRP will also bind LRP2" (remarks, p. 7, second paragraph) and that given the structural and functional variation between LRP and LRP2 it would be improper to make such an assumption.

3) The references cited by the examiner have been improperly combined because they do not deal with the receptor mentioned in the claims, and have not been shown to be either equivalent or interchangeable (remarks, p. 10, last complete paragraph).

4) The cited references fail to show a reasonable expectation of success on the part of the artisan of ordinary skill.

With respect to 1), applicant argues that the examiner is mistaken in assuming that any and all ligands of LRP will cross the blood brain barrier. Applicant argues that Fillebeen does not teach this, and such a conclusion would be improper. The examiner notes that Fillebeen states that "[w]e demonstrated that Lf transcytosis was mediated by LRP because 70% of the Lf traffic was inhibited by RAP" (p. 7016, second column lines 7 – 9). It is Fillebeen who provides the positive statement on the role of LRP in transcytosing ligands across the BBB. Fillebeen specifically measured Lf transcytosis, not RAP transcytosis, but since RAP is stated by Fillebeen to be "known to interact with LRP and block the binding of any kind of LRP ligand" (p. 7014 second column first complete paragraph), it is reasonable to conclude that RAP occupies the ligand binding site of LRP. Applicant argues that the reference by Vash (1998, Blood 92:3277-3285, submitted as Exhibit B) teaches that RAP "appears to cause a conformational change in the LRP protein preventing it from binding other ligands", suggesting that RAP binds to a different site on LRP than lactoferrin. The examiner has carefully reviewed the reference by Vash and has concluded that it supports the examiner's position that one of ordinary skill in the art would conclude that RAP binds to LRP, which Fillebeen teaches transports molecules across the BBB. Vash teaches "that RAP, PAI-1, and lactoferrin each inhibit the binding of the others, suggesting that at this site in LRP, RAP acts as a competitive, rather than an allosteric, inhibitor of PAI-1 and lactoferrin binding" (abstract, final sentence). Additionally Vash presents data from a series of experiments which support this conclusion (p. 3280, second column), and states that his data indicate that "a single binding site on LRP is capable of binding three different proteins, including RAP" (p. 3281, second column). Vash also argues against a

competing hypothesis that RAP binds to two distinct locations on LRP (p. 3283, second column, first complete paragraph). Thus the reference by Vash supports the conclusion from Fillebeen that RAP binds to the transcytosing receptor LRP. In fact, given that Vash indicates that the same region of LRP binds to both lactoferrin and RAP, this reference supports the examiner's conclusion that RAP would be transported across the BBB by LRP.

With respect to 2) above, applicant argues that given the structural and functional differences between LRP, which Fillebeen teaches is a BBB-transcytosing receptor, and megalin (also called LRP2), recited in independent claims 17 – 20 3 and to which the relevant fragment of SEQ ID NO:1 or a variant thereof is required to bind, one of ordinary skill in the art would not expect that ligands of LRP would also be ligands of LRP2. Thus, according to applicant's arguments, the artisan of ordinary skill would not be motivated to select an LRP2-binding fragment, so the invention must be non-obvious.

Applicant's argument has been fully considered but it is not persuasive. The examiner concedes that there are structural differences between LRP and LRP2. However, claims 17 – 18 as written are drawn to administration of a fusion protein comprising a RAP fragment which "consists of an amino acid sequence at least 80% identical to amino acids 221 – 323 of RAP (SEQ ID NO:1), wherein said RAP polypeptide retains binding to LRP2". Claim 19 is similar except that it does not explicitly require the megalin-binding function, but merely requires the requisite degree of structural identity. The examiner is unable to determine whether residues 203 – 319, taught by Saenko to bind LRP, also bind to megalin as claimed because both the prior art and the instant specification are silent as to the residues of RAP necessary for LRP2 binding. At p. 7 of the remarks, applicant argues that certain structural and functional differences between LRP and LRP2 indicate that binding to one does not necessarily indicate binding to the other will occur. Given the evidence of record, the examiner cannot determine whether residues 203 – 319 taught by Saenko will bind to megalin as claimed. However, once a prima facie case of inherency has been set forth, as is the case here, the burden is on applicant to provide evidence of non-obviousness; see MPEP § 2112(V). Arguments by an attorney cannot take the place of evidence when the latter is required; see MPEP § 2145(i).

Given that the fragment taught by Saenko meets all the structural limitations of the RAP fragment, the receptor-binding property is presumed to be provided for; see MPEP § 2112(III). The references cited herein (Pardridge, Fillebeen, Neels, and Saenko) provide guidance and motivation to the artisan of ordinary skill to select the LRP-binding fragment consisting of

residues 203 – 319 of RAP taught by Saenko to use as the BBB-transporting agent. A rationale or reason to combine prior art references can be different from applicant's; see MPEP § 2144(IV). Here, given the teachings of Fillebeen and Neels which are on point to transcytosing properties of LRP and LRP-binding properties of RAP, the examiner has concluded that it would have been obvious to one of ordinary skill to select the known LRP binding fragment (residues 203 – 319) taught by Saenko, thereby arriving at a method of administering a fusion protein consisting of these residues of SEQ ID NO:1, which share more than 80% identity with residues 221 – 323, and a therapeutic agent, thereby arriving at the inventions of claims 17 – 19. The rationale for selecting an LRP-binding fragment of RAP has been thoroughly described. Although the artisan of ordinary skill may not know whether this fragment is also a megalin-binding fragment, the artisan would nonetheless be motivated to select this fragment, arriving at the inventions of claims 17 - 19.

With respect to 3), applicant argues that the references cited by the examiner have been improperly combined because they do not deal with the receptor mentioned in the claims, and have not been shown to be either equivalent or interchangeable. Applicant's argument has been fully considered but it is not persuasive. As set forth in the preceding paragraph, an examiner's rationale for combining teachings in references can be different from applicant's. The examiner has set forth a prima facie case of obviousness as to why one of ordinary skill in the art would have been motivated to select the specific RAP fragment taught by Saenko, based on its LRP binding activities. The product is within the scope of the product (RAP fragment at least 80% identical to recited residues of SEQ ID NO:1) recited in claims 17 – 19. The examiner is unable to determine whether or not the product has the property recited in the claim, namely binding to LRP2. Clearly a receptor-binding region is present, according to Saenko it binds LRP. Thus it is reasonable that the product also binds a different lipoprotein related receptor, namely megalin. The examiner concedes that megalin is not mentioned in the references cited, however no evidence of record allows one to determine which regions of RAP within residues 221 – 323 are the megalin (or LRP2) binding region.

With respect to 4), at p. 11 of the remarks, applicant argues that the cited references fail to provide a reasonable expectation of success. The examiner disagrees. The reference by Fillebeen clearly shows that the authors' conclusion was that LRP is the receptor responsible for BBB transcytosis, Neels provides further teachings on the ligand-binding regions of LRP, and Saenko teaches a specific fragment that binds to LRP. Applicant cites the reference by Marzolo

submitted with the instant response as suggesting that LRP is expressed on the wrong side of the BBB. The examiner disagrees with applicant's characterization of the reference. Marzolo did not use BBB cells, or even a model of them. Rather the authors used kidney cells and studied expression of LRP there. It is not immediately apparent how kidney cells expression patterns related to BBB transport. The examiner is of course aware that kidneys transport certain factors across cell membranes, however there is not currently evidence of record indicating that kidney tubule cells are a reasonable model of BBB function. The reference by Fillebeen, on the other hand, uses brain epithelial cells (which make up the BBB *in vivo*) and provides evidence that LRP is in fact the receptor which transports ligands across the BBB. Note that the standard to be used in determinations of obviousness is not absolute certainty, but rather a reasonable expectation of success (MPEP § 2143.03(I) and (II)).

It is believed that all of applicant's arguments with respect to non-obviousness have been addressed. For the reasons stated above, the cited references would have motivated an artisan of ordinary skill to make a fusion protein consisting of a RAP fragment at least 80% identical to residues 221 - 323 of SEQ ID NO:1 and a therapeutic agent, and to administer it to a subject, as encompassed by claims 17 - 19. Applicant did not separately traverse the examiner's determination that the limitations of claims 21 and 58 - 62 are taught or suggested by the references cited.

Allowable Subject Matter

7. The prior art does not teach or suggest administration of conjugates consisting of residues 221 - 323 of SEQ ID NO:1 and a therapeutic agent.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1649

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./

Patent Examiner, Art Unit 1649

August 12, 2008